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APPLICATION NO.	F	ILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/902,772		07/12/2001	Masahiro Iwamoto	46124-5001-01	1361
9629	7590	01/15/2003			
		& BOCKIUS LLP		EXAMI	NER
WASHINGT		IA AVENUE NW 20004		SCHNIZER,	HOLLY G
				ART UNIT	PAPER NUMBER
				1653	li
				DATE MAILED: 01/15/2003	N

Please find below and/or attached an Office communication concerning this application or proceeding.





Applicant(s)

09/902,77	2
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Examiner Holly Schnizer

WAMOTO ET AL
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**Art Unit** 

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-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --**Period for Reply** 

### A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.

Office Action Summary

- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication. Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any

earned patent term adjustment. See 37 0	CFR 1.704(b).	communication, even in unitery med, may reduce any
1) Responsive to commun	ication(s) filed on <u>01 Novemb</u> e	<u>er 2002</u> .
2a) This action is <b>FINAL</b> .	2b)⊠ This action	is non-final.
closed in accordance w		ept for formal matters, prosecution as to the merits is Quayle, 1935 C.D. 11, 453 O.G. 213.
Disposition of Claims		
4)⊠ Claim(s) <u>1,5 and 20-39</u> i	s/are pending in the application	n.
		e withdrawn from consideration.
5) Claim(s) is/are all	owed.	
6)☐ Claim(s) <u>32,34 and 36-3</u>	<del>-</del>	
7)⊠ Claim(s) <u>34</u> is/are object	ed to.	
8) Claim(s) are subject	ect to restriction and/or election	n requirement.
Application Papers		
9) The specification is objec	•	_
10) The drawing(s) filed on _		· · · · · · · · · · · · · · · · · · ·
		y(s) be held in abeyance. See 37 CFR 1.85(a).
		approved b) disapproved by the Examiner.
	wings are required in reply to this	Office action.
12) The oath or declaration is	<u> </u>	
Priority under 35 U.S.C. §§ 119 a	•	
		under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ⊡		
1. Certified copies of	the priority documents have b	een received.
2. Certified copies of	the priority documents have b	een received in Application No
application from	n the International Bureau (Po	
* See the attached detailed	Office action for a list of the co	ertified copies not received.
14) ☐ Acknowledgment is made	of a claim for domestic priority	under 35 U.S.C. § 119(e) (to a provisional application).
		application has been received. y under 35 U.S.C. §§ 120 and/or 121.
Attachment(s)	'	,
1) Notice of References Cited (PTO-89. 2) Notice of Draftsperson's Patent Draw 3) Information Disclosure Statement(s)	ring Review (PTO-948)	4) Interview Summary (PTO-413) Paper No(s) 5) Notice of Informal Patent Application (PTO-152) 6) Other:

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### **DETAILED ACTION**

### Status of the Claims

Applicant's election of Group II, Claims 32, 34, and 36-38, drawn to polynucleotides encoding C-11 in Paper No. 10 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Therefore, Claims 1, 5, and 20-39 are pending, Claims 1, 5, 20-31, 33, 35, and 39 are withdrawn from consideration as being drawn to non-elected subject matter, and Claims 32, 34, and 36-38 have been considered in this Office Action.

## Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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Claims 32 and 34 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 6,294,354.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See e.g., In re Berg, 140 F.3d 1428, 46USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Here, claims 1 and 2 of U.S. Patent No. 6,294,354 recites a nucleic acid encoding a C11 protein comprising the amino acids as set forth in SEQ ID NO:2 and the nucleic acid sequence of SEQ ID NO:1. These nucleic acids differ from that of the composition comprising an c-erg gene claimed in Claims 32 and a composition comprising a C-11 gene or a c-erg gene of Claim 34 of the present application only in that SEQ ID NO:1 is missing nucleotides 655-735 of the c-erg gene. However, Patent No. 6,294,354 also teaches the sequence of the c-erg gene and teaches that both C-11 and c-erg, when introduced into osteoblasts, inhibit calcification (see abstract of the patent). Therefore, it would have been obvious to modify the C-11 sequence to add the additional nucleotides 655-735 of the c-erg gene in order to express the c-erg protein for use in studying cartilage morphogenesis. One of ordinary skill would have been motivated to express both C-11 and c-erg in order to better understand how the protein structures affect cartilage morphogenesis and to explore the differences in tissue

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expression of the two genes in order to better understand the role of the erg genes during chicken embryogenesis.

## Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 32 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Dhordain et al. (Mech. Dev. (1995) 50: 17-28; cited in IDS of Paper No. 6).

Dhordain et al. teach the cloning of the chicken erg gene (ck-erg) (see lines 6-7 of abstract). The erg gene composition of Dhordain et al. appears to be indistinguishable from the pharmaceutical compositions of present Claims 32 and 34. The erg gene disclosed in Dhordain et al. appears to have a sequence identical to SEQ ID NO: 1 and 3 of the present invention except that it contains an extra 81 nucleotides from position 655-735 of SEQ ID NO:1 (see sequence alignment attached to this Office Action).

# Claim Rejections - 35 USC § 112

\*\*\*It is noted that the following enablement rejection contains two separate issues.

Claims 32 and 34 are deemed to lack enablement because of the intended use of the



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claimed compositions in methods of gene therapy. Claim 36 lacks enablement because the primer of (b) comprising the complement of nucleotides 645-662 as set forth in SEQ ID NO:1 (as required in the last lines of the claim) could not be used to amplify the nucleic acid encoding the protein having the sequence of SEQ ID NO:4. The rejections have been separated into two parts and are as follows:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32 and 34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include: the nature of the invention; the breadth of the claims; the predictability or unpredictability of the art; the amount of direction or guidance presented; the presence or absence of working examples; the quantity of experimentation necessary; the state of the prior art; and, the relative skill of those skilled in the art;

Each factor is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

Breadth of the Claims

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The claims are drawn to <u>pharmaceutical</u> compositions comprising genes. Thus, the claims encompass the <u>intended use of the claimed compositions in gene therapy</u>.

Nature of the Invention

A review of the Specification appears to indicate that the invention is the discovery of a "novel isoform of the c-erg gene (herein referred to as 'C-11 gene' or 'C11 gene') which is an erg gene derived from chicken" (p. 5, lines 1-5 of Specification). The Amount of Direction or Guidance Presented and the Presence or Absence of Working examples:

The present Specification does not provide any working examples of methods of gene therapy using the disclosed nucleotide sequences and does not provide any guidance as to any protocols for using the disclosed sequences in any gene therapy methods.

State of the prior art and relative skill of those in the art

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by recently published reviews. Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist

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including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). More recently, Romano et al (Stem Cells 18:19-39, 2000) reviewed the general state of gene therapy, and found that the problems relating to gene delivery and expression discussed above persisted. See entire document, especially, last sentence of abstract; last sentence of column 1 on page 20 to column 2, line 6; page 21, column 1, lines 1-9 and 18-21; sentence bridging columns 1 and 2 on page 21; and first sentence of last paragraph on page 21. This idea was echoed by Somia and Verma (Nature Reviews/Genetics 1: 9199, 11/2000), who noted that delivery vehicles still represented the Achilles heel of gene therapy, and that no single vector existed that had all of the attributes of an ideal gene therapy vector. See page 91, column 1, lines 5-13 of first paragraph.

The predictability or unpredictability of the art

The art of gene therapy is highly unpredictable as evidenced by the problems discussed in the paragraph above.

In consideration of each of the above factors, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented.

Absent factual data to the contrary, the amount and level of experimentation needed is undue.

The examiner notes that this enablement rejection can be overcome by deleting the term "pharmaceutical".

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Claims 36-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 36 encompasses a nucleic acid which is complementary to at least a portion of a nucleic acid encoding a C-11 protein wherein the nucleic acid can be selected from (b) a nucleotide primer capable of amplifying a nucleic acid encoding a protein comprising amino acids derived from SEQ ID NO:4 wherein the complementary nucleic acid (b) comprises the complement of nucleotides 645-662 as set forth in SEQ ID NO:1. As stated in the Specification (p. 9), the C-11 gene (SEQ ID NO:1) lacks nucleotides 655-735 of c-erg (SEQ ID NO:3 which encodes SEQ ID NO:4). Therefore, it is impossible to use a primer for nucleotides 645-662 as set forth in SEQ ID NO:1 to amplify the polynucleotide encoding the protein of SEQ ID NO:4 since the primer sequence lacks nucleotides that are part of the sequence that encodes SEQ ID NO:4 (see sequence alignment attached to this Office Action for an example of a comparison of the C-11 sequence (SEQ ID NO:1) to the c-erg sequence (Db sequence; representative of SEQ ID NO:3 which encodes SEQ ID NO:4).

Claim 36 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably



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convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It appears that the specific nucleic acids claimed (those selected from the group of parts (a), (b), or (c) that comprise the complement of nucleotides 645-662 of SEQ ID NO:1 constitute new matter. Claim 36 was added in the Second Preliminary Amendment filed September 6, 2001. The Specification as originally presented does not appear to describe primers or probes comprising specifically the complement of nucleotides 645-662 of SEQ ID NO:1. Correction is required.

### **Conclusions**

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer January 13, 2003 CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1800

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REFERENCE
AUTHORS
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Direct Submission
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Mesodermal expression of the chicken erg gene associated with
precartilaginous condensation and cartilage differentiation
Mech. Dev. 50 (1), 17-28 (1995)
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SKMSFRYPQDWLSQPPARVTIKMECHPNQVNGSRNSFDDCSYMGGKKYVSSSDNVGM
NYGSYMEEKHIPPPNMTTNERRVIYPADPTLMSTDHVRQMLEMAVKEYGLPDVDILF
QNIDGKELCKWTKDDFQRLTPSYNADJILLSHLHYLRSTPLPHLTSDDVDKALQNSPRL
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/db_xref="SWISS-PROT:090837"
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/dev_stage="adult"
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299	ACCATGCACACCCCCAGAAGATGAACTTTGTAGCTCCCCATCCCCCTGCTTTGCCCGTAA 1:	1240	Оу
320	CTCACCCTCCAGAATCATCCATGTACAAATACCCATCAGACCTCCCCTACATGAGTTCCT 1:	1261	DЬ
239	TCACCCTCCAGAATCATCCATGTACAAATACCCATCAGACCTCCCCTACATGAGTTCCT 1	1180	Ωу
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179	GATTTCCACGGAATCGCTCAGGCCCTCCAGC 1	1120	Qy
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.119	TATGACAAACTCAGCCGTGCACTTCGCTACTATGACAAAAATATTATGACTAAAG 1	1060	Qy
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059	GACAGACCCTGATGAAGTGGCTTCGGCGTTTGGGGAAGAGGAAAAAGCAAAACCTAACATGA 1	1000	Оу
080	TGTCGGACAGCTCCAACTCCAACTGCATCACCTGGGAGGGCACAAATGGGGAGTTCAAGA 1	1021	Дb
99	GTCGGACAGCTCCAACTCCAACTGCATCACCTGGGAGGGCACAAAATGGGGGAGTTCAAGA 9	940	Qy
020	GCCGTCTTGCAAATCCAGGGAGTGGGCAGATACAGCTATGGCAGTTCCTACTGGAGCTTC 1	961	Db
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60	CAAAACAGAAGACCAGCGTCCTCAGTTAGATCCTTATCAGATTCTTGGACCGACC	901	DЬ
79.	AACAGAAGACCAGCGTCCTCAGTTAGATCCTTATCAGATTCTTGGACCGACC	820	Qy
00	GACGAGTCACAGCCATCCCCACTCAGTCAAAAAGCTACCCAACCATCATCTTCAACAGTGC 9(	841	DЬ
19	GACGAGTCACAGCCATCCCACTCAGTCAAAAAGCTACCCAACCATCATCTTCAACAGTGC 8	760	Qy
40	CAACGCAAAGAATAACAACAACGACAGATTTACCTTATGAGCAAGCGAGGAGATCAGCGT 84	781	Db
59	AACGCAAAGAATAACAACAAGGCCAGATTTACCTTATGAGCAAGCGAGGAGATCAGCGT 7	700	Οу
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54	ACGCAGATATCCTCCTGTCACACCTACACTACCTCAGAGAGA6	21	Qy
00	AACATTGATGGGAAAGAGTTGTTGTAAAATGACCAAAGATGACTTCCAGAGACTCA	541	DЬ
00	CCAGAACATTGATGGGAAAGAGTTGTGTAAAATGACCAAAGATGACTTCCAGAGACTCA 6	541	Оу
40	GGCAGTGGCTGGAGTGAAGGAGTATGGTCTTCCAGACGTGGACATCTTGTTGT 5	481	Дb
40	GCAGTGGCTGGAGTGGGCAGTGAAGGAGTATGGTCTTCCAGACGTGGACATCTTGTTGT 5	481	Qy
80	CCAATGAACGAAGAGTTATTGTGCCAGCAGATCCTACGTTATGGAGCACAGACCATGTAC 4		Db
80	CAATGAACGAAGAGTTATTGTGCCAGCAGATCCTACGTTATGGAGCACAGACCATGTAC 4		Qy
20	TTGGGATGAACTATGGAAGCTACATGGAAGAGAAGCATATTCCGCCTCCAAATATGACAA 4	361	Db
20	TGGGATGAACTATGGAAGCTACATGGAAGAGAAGCATATTCCGCCTCCAAATATGACAA 4	361	VΩ
60	ATTCACCTGATGACTGCAGCGTGGCAAAAGGAGGGAAAATGGTTAGCAGTTCAGACAATG 3	301	Db
60	TTCACCTGATGACTGCAGCGTGGCAAAAGGAGGGAAAATGGTTAGCAGTTCAGACAATG 3	301	Qy
00	CCCCGGCCAGAGTTACCATTAAGATGGAGTGTAACCCAGACCAGGTTAATGGGTCAAGGA 3	. 241	Db
00	CCCGGCCAGAGTTACCATTAAGATGGAGTGTAACCCAAACCAGGTTAATGGGTCAAGGA 3	241	Qy

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MHARWIDLPYEEPRSTWTGHSHPTPOSKAAQDSPSYTVPKTEDGPAQLDPYQILGPTS
SRLANPGSGQ10LMWGTLLELLSDSSUSNCTTWBGTNGEFKMTDPDEVARMGERKKKP
MMNYDKLSRALRYYYDKNIMTKVHGKRYAYKFDFHGIAQALQPHPPESSLYKYPSDLP
                                                                                                                                                                                                                                                        /translation="MASTIKEALSVVSKDQSLFECAYGTPHLAKTEMTASSSSDYGQT
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SYGSYMEEKHMPPPNMTTNERRVIVPADPTLMSTDHVRQWLEMAVKEYGLLDVDVLLF
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LGTYY"
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/protein_id="BAB62744.1"
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/note="similar to human erg1"
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/tissue_type="liver"
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